

COMBINATIONS OF FORMOTEROL AND FLUTICASONE PROPIONATE FOR ASTHMA

This invention relates to combinations of a beta-2 agonist and a steroid and their use for the treatment of inflammatory or obstructive airways diseases.

Formoterol, N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)-ethyl)phenyl]formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases. Fluticasone propionate, S-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate, an anti-inflammatory corticosteroid, is described in US4335121.

It has now surprisingly been found that a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained by using a composition containing formoterol, or a salt or solvate thereof, and fluticasone propionate. For instance, it is possible using such a composition to reduce the dosages of fluticasone propionate required for a given therapeutic effect considerably compared with those required using treatment with fluticasone propionate alone, thereby minimising possibly undesirable side effects. In particular, it has been found that compositions containing formoterol and fluticasone propionate induce an anti-inflammatory activity which is significantly greater than that induced by formoterol or fluticasone propionate alone and that the amount of fluticasone propionate needed for a given anti-inflammatory effect may be significantly reduced when used in admixture with formoterol, thereby reducing the risk of undesirable side effects from the repeated exposure to the steroid involved in the treatment of inflammatory or obstructive airways diseases.

Furthermore, using the compositions of the invention, medicaments which have a rapid onset of action and a long duration of action may be prepared. Moreover, using the compositions of the invention, medicaments which result in a significant improvement in lung function may be prepared. In another aspect, using the compositions of the invention, medicaments which provide improved control of obstructive or inflammatory airways diseases, or a reduction in exacerbations of such diseases, may be prepared. In a further aspect, using compositions of the invention, medicaments which can be used on demand in rescue treatment of obstructive or inflammatory airways diseases, or which reduce or eliminate the need for treatment with short-acting rescue medicaments such as salbutamol or

terbutaline, may be prepared; thus medicaments based on compositions of the invention facilitate the treatment of an obstructive or inflammatory airways disease with a single medicament.

Accordingly, in one aspect, the present invention provides a pharmaceutical composition comprising (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) fluticasone propionate.

In another aspect, the present invention provides a method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising (A) and (B) as hereinbefore defined.

In a further aspect, the present invention provides a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B) as hereinbefore defined together with a pharmaceutically acceptable carrier.

In a yet further aspect, the present invention provides a pharmaceutical composition for use in the treatment of an inflammatory or obstructive airways disease comprising (A) and (B) as hereinbefore defined.

The present invention still further provides the use of a pharmaceutical composition comprising (A) and (B) as hereinbefore defined for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

Pharmaceutically acceptable salts of formoterol include, for example, salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarboxylic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acids.

Component (A) may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. It may be in the form of a solvate, for example a hydrate, thereof, for example as described in US3994974 or US5684199, and may be present in a particular crystalline form, for example as described in

WO95/05805. Preferably, component (A) is formoterol fumarate, especially in the form of the dihydrate.

Administration of the pharmaceutical composition as hereinbefore described is preferably by inhalation, in which case (A) and (B) are in inhalable form. The inhalable form of the composition may be, for example, an atomizable composition such as an aerosol comprising the active ingredients, i.e. (A) and (B), in solution or dispersion in a propellant, or a nebulizable composition comprising a dispersion of the active ingredients in an aqueous, organic or aqueous/organic medium. For example, the inhalable form of the pharmaceutical composition may be an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant. In another example, the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium.

An aerosol composition suitable for use as the inhalable form of the composition of the invention may comprise the active ingredients in solution or dispersion in a propellant, which may be chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more such hydrocarbons, and halogen-substituted hydrocarbons, for example fluorine-substituted methanes, ethanes, propanes, butanes, cyclopropanes or cyclobutanes, particularly 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where (A) and/or (B) are present in suspension in the propellant, i.e. where present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those lubricants and surfactants known in the art. Other suitable aerosol compositions include surfactant-free or substantially surfactant-free aerosol compositions. The aerosol composition may contain up to about 5% by weight, for example 0.002 to 5%, 0.01 to 3%, 0.015 to 2%, 0.1 to 2%, 0.5 to 2% or 0.5 to 1%, by weight of the mixture of (A) and (B), based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by weight of the aerosol composition. The aerosol composition may also contain a co-solvent such as ethanol in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device.

In another embodiment of the invention, the inhalable form is a dry powder, i.e. (A) and (B) are present in a dry powder comprising finely divided (A) and (B) optionally together with a finely divided pharmaceutically acceptable carrier, which is preferably present and may be

one or more materials chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. An especially preferred carrier is lactose, particularly in the form of the monohydrate. The dry powder may be in capsules of gelatin or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of the mixture of (A) and (B) together with the carrier in amounts to bring the total weight of powder in each capsule to from 5 mg to 50 mg. Alternatively, the dry powder may be contained in a reservoir of a multi-dose dry powder inhalation device.

In the finely divided particulate form of the composition of the invention, (A) and (B) may each have an average particle diameter of up to about 10  $\mu\text{m}$ , for example 0.1 to 5  $\mu\text{m}$ , preferably 1 to 5  $\mu\text{m}$ . In the aerosol composition where (A) and/or (B) are present in particulate form, (A) and/or (B) may have an average particle diameter of up to about 10  $\mu\text{m}$ , for example 0.1 to 5  $\mu\text{m}$ , preferably 1 to 5  $\mu\text{m}$ . The solid carrier, where present, generally has a maximum particle diameter of 300  $\mu\text{m}$ , preferably 212  $\mu\text{m}$ , and conveniently has a mean particle diameter of 40 to 100  $\mu\text{m}$ , preferably 50 to 75  $\mu\text{m}$ . The particle size of the active ingredients (A) and (B), and that of a solid carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray-drying, lyophilisation or recrystallisation from supercritical media.

The inhalable pharmaceutical composition of the invention may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a pharmaceutical composition comprising (A) and (B) as hereinbefore described in inhalable form as hereinbefore described in association with one or more inhalation devices. In a further aspect, the invention provides an inhalation device containing a pharmaceutical composition comprising (A) and (B) as hereinbefore described in inhalable form as hereinbefore described.

Where the inhalable form of the composition of the invention is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100  $\mu\text{l}$ , e.g. 25 to 50  $\mu\text{l}$ , of the composition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them

aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992. Where the inhalable form of the composition of the invention is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, for example an electronically controlled device such as an AERx (ex Aradigm, US) or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100  $\mu$ l, than conventional nebulizers. Where the inhalable form of the composition of the invention is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dosage unit of the dry powder or a multidose dry powder inhalation (MDPI) device adapted to deliver, for example, 5-25 mg of dry powder per actuation. Suitable such dry powder inhalation devices are well known. For example, a suitable device for delivery of dry powder in encapsulated form is that described in US3991761, while a suitable MDPI device is that described in WO97/20589.

The weight ratio of formoterol, or salt or solvate thereof, to fluticasone propionate may be, in general, from 3:1 to 1:3000, for example from 2:1 to 1:2000, from 1:1 to 1: 1000, from 1:2 to 1:500 or from 1:5 to 1:50. More usually, this ratio is from 1:10 to 1 to 1:25, for example from 1:10 to 1:20. Specific examples of this ratio, to the nearest whole number, include 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19, 1:20, 1:21, 1:22, 1:23, 1:24 and 1:25. The above weight ratios apply particularly where (A) is formoterol fumarate dihydrate. Thus, since the molecular weights of formoterol fumarate dihydrate and fluticasone propionate are 840.9 and 500.6 respectively, the corresponding molar ratios of (A) to (B) may be, in general, from 1.79:1 to 1:5017, for example from 1.2:1 to 1:3345, from 0.6:1 to 1:1672, from 1:3.34 to 1:836 or from 1:8.36 to 1:83.6; more usually from 1:16.7 to 1:41.8, for example from 1:16.7 to 1:33.4; specific examples of the molar ratio being 1:16.7, 1:18.4, 1:20.1, 1:21.7, 1:23.4, 1:25.1, 1:26.8, 1:28.4, 1:30.1, 1:31.8, 1:33.4, 1:35.1, 1:36.8, 1:38.5, 1:40.1, and 1:41.8.

A suitable daily dose of formoterol, or salt or solvate thereof, particularly as formoterol fumarate dihydrate, for inhalation in a composition of the invention may be from 1 to 72  $\mu$ g, for example from 1 to 60  $\mu$ g, generally from 3 to 50  $\mu$ g, preferably from 6 to 48  $\mu$ g, for instance from 6 to 24  $\mu$ g. A suitable daily dose of fluticasone propionate for inhalation in a

composition of the invention may be from 25 to 3000  $\mu\text{g}$ , for example from 25 to 2000  $\mu\text{g}$ , from 50 to 2000  $\mu\text{g}$ , preferably from 100 to 1000  $\mu\text{g}$ , for instance from 200 to 1000  $\mu\text{g}$  or from 200 to 500  $\mu\text{g}$ . The precise dose used will of course depend on the condition to be treated, the patient and the efficiency of the inhalation device. The formulation of a composition of the invention and its frequency of administration may be chosen accordingly. A suitable unit dose of formoterol component (A), particularly as formoterol fumarate dihydrate, in a composition of the invention may be from 1 to 72  $\mu\text{g}$ , for example from 1 to 60  $\mu\text{g}$ , generally from 3 to 48  $\mu\text{g}$ , preferably from 6 to 36  $\mu\text{g}$ , especially from 12 to 24  $\mu\text{g}$ . A suitable unit dose of fluticasone propionate (B) in a composition of the invention may be from 25  $\mu\text{g}$  to 500  $\mu\text{g}$ , for example from 50  $\mu\text{g}$  to 400  $\mu\text{g}$ , preferably from 100  $\mu\text{g}$  to 300  $\mu\text{g}$ , especially from 150 to 250  $\mu\text{g}$ . These unit doses may suitably be administered once or twice daily in accordance with the suitable daily dose mentioned hereinbefore. For on demand usage, a dosage unit containing 6  $\mu\text{g}$  or 12  $\mu\text{g}$  of (A) and 50  $\mu\text{g}$  or 100  $\mu\text{g}$  of fluticasone propionate (B) is preferred.

In one preferred embodiment of the invention, when the pharmaceutical composition of the invention is a dry powder in a capsule containing a unit dose of (A) and (B), for example for inhalation from a single capsule inhaler, the capsule may suitably contain, where (A) is formoterol fumarate dihydrate, from 3  $\mu\text{g}$  to 36  $\mu\text{g}$  of (A), preferably from 6  $\mu\text{g}$  to 24  $\mu\text{g}$  of (A), especially from 12  $\mu\text{g}$  to 24  $\mu\text{g}$  of (A), and from 25  $\mu\text{g}$  to 500  $\mu\text{g}$  of (B), preferably from 50  $\mu\text{g}$  to 250  $\mu\text{g}$  of (B), especially from 100 to 250  $\mu\text{g}$  of (B), together with a pharmaceutically acceptable carrier as hereinbefore described in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50 mg, for example 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg or 50 mg, preferably 20 to 25 mg, especially 25 mg.

In another preferred embodiment of the invention, the pharmaceutical composition of the invention is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver 3 mg to 25 mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is formoterol fumarate dihydrate, a powder comprising, by weight, 3 to 36 parts, preferably 6 to 24 parts, especially 12 to 24 parts of (A); 25 to 500 parts, preferably 50 to 400 parts, especially 100 to 250 parts of (B); and 2464 to 24972 parts, preferably 4464 to 14972 parts, especially 4464 to 9972 parts of a pharmaceutically acceptable carrier as hereinbefore described.

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis and emphysema, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalcosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

The invention is illustrated by the following Examples, in which parts are by weight unless stated otherwise.

Example 1 - Aerosol Composition for Metered Dose Inhaler

Ingredient	% by weight
Formoterol fumarate dihydrate	0.012
Fluticasone propionate	0.250
Ethanol (absolute)	2.500
HFA 227	60.768
HFA134a	36.470

Example 2 - Dry Powder

Ingredient	% by weight
Formoterol fumarate dihydrate	0.048
Fluticasone propionate	1.000
Lactose monohydrate	98.952

Example 3

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing 12 parts of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1.5 $\mu$ m in an air-jet mill, 250 parts of fluticasone propionate which has been similarly ground to a mean particle diameter of 1.5 $\mu$ m and 4738 parts of lactose monohydrate having a particle diameter below 212 $\mu$ m.

Examples 4 - 92

Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Fluticasone Propionate (Parts)	Lactose Monohydrate (Parts)
4	12	50	4938
5	12	100	4888
6	12	150	4838

7	12	200	4788
8	6	50	4944
9	6	100	4894
10	6	150	4844
11	6	200	4794
12	6	250	4744
13	18	50	4932
14	18	100	4882
15	18	150	4832
16	18	200	4782
17	18	250	4732
18	24	50	4926
19	24	100	4876
20	24	150	4826
21	24	200	4776
22	24	250	4726
23	30	50	4920
24	30	100	4870
25	30	150	4820
26	30	200	4770
27	30	250	4720
28	36	50	4914
29	36	100	4864
30	36	150	4814
31	36	200	4764
32	36	250	4714
33	6	50	9944
34	6	100	9894
35	6	150	9844
36	6	200	9794
37	6	250	9744
38	12	50	9938
39	12	100	9888
40	12	150	9838
41	12	200	9788

42	12	250	9738
43	18	50	9932
44	18	100	9882
45	18	150	9832
46	18	200	9782
47	18	250	9732
48	24	50	9926
49	24	100	9876
50	24	150	9826
51	24	200	9776
52	24	250	9726
53	30	50	9920
54	30	100	9870
55	30	150	9820
56	30	200	9770
57	30	250	9720
58	36	50	9914
59	36	100	9864
60	36	150	9814
61	36	200	9764
62	36	250	9714
63	6	50	14944
64	6	100	14894
65	6	150	14844
66	6	200	14794
67	6	250	14744
68	12	50	14938
69	12	100	14888
70	12	150	14838
71	12	200	14788
72	12	250	14738
73	18	50	14932
74	18	100	14882
75	18	150	14832
76	18	200	14782

77	18	250	14732
78	24	50	14926
79	24	100	14876
80	24	150	14826
81	24	200	14776
82	24	250	14726
83	30	50	14920
84	30	100	14870
85	30	150	14820
86	30	200	14770
87	30	250	14720
88	36	50	14914
89	36	100	14864
90	36	150	14814
91	36	200	14764
92	36	250	14714

### Example 93

Gelatin capsules suitable for use in a capsule inhaler such as that described in US3991761 are prepared, each capsule containing a dry powder obtained by mixing 12 $\mu$ g of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1 to 5 $\mu$ m in an air jet mill, 250 $\mu$ g of fluticasone propionate which has been similarly ground to a mean particle diameter of 1 to 5 $\mu$ m and 24738 $\mu$ g of lactose monohydrate having a particle diameter below 212 $\mu$ m.

### Examples 94 - 152

Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Fluticasone Propionate (Parts)	Lactose Monohydrate (Parts)
94	12	50	24938
95	12	100	24888

96	12	150	24838
97	12	200	24788
98	6	50	24944
99	6	100	24894
100	6	150	24844
101	6	200	24794
102	6	250	24744
103	18	50	24932
104	18	100	24882
105	18	150	24832
106	18	200	24782
107	18	250	24732
108	24	50	24926
109	24	100	24876
110	24	150	24826
111	24	200	24776
112	24	250	24726
113	30	50	24920
114	30	100	24870
115	30	150	24820
116	30	200	24770
117	30	250	24720
118	36	50	24914
119	36	100	24864
120	36	150	24814
121	36	200	24764
122	36	250	24714
123	6	50	19944
124	6	100	19894
125	6	150	19844
126	6	200	19794
127	6	250	19744
128	12	50	19938
129	12	100	19888
130	12	150	19838

131	12	200	19788
132	12	250	19738
133	18	50	19932
134	18	100	19882
135	18	150	19832
136	18	200	19782
137	18	250	19732
138	24	50	19926
139	24	100	19876
140	24	150	19826
141	24	200	19776
142	24	250	19726
143	30	50	19920
144	30	100	19870
145	30	150	19820
146	30	200	19770
147	30	250	19720
148	36	50	19914
149	36	100	19864
150	36	150	19814
151	36	200	19764
152	36	250	19714

Examples 153 - 176

Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (Parts)	Fluticasone Propionate (Parts)	Lactose Monohydrate (Parts)
153	6	25	2969
154	6	50	2944
155	6	100	2894

156	6	150	2844
157	6	200	2794
158	6	250	2744
159	12	25	2963
160	12	50	2938
161	12	100	2888
162	12	150	2838
163	12	200	2788
164	12	250	2738
165	12	300	2638
166	12	350	2588
167	12	400	2538
168	24	25	2951
169	24	50	2926
170	24	100	2876
171	24	150	2826
172	24	200	2776
173	24	250	2726
174	24	300	2676
175	24	350	2626
176	24	400	2576

### Examples 177-216

Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (μg)	Fluticasone Propionate (μg)	Lactose Monohydrate (μg)
177	6	25	14969
178	6	50	14944
179	6	100	14894
180	6	150	14844
181	6	200	14794
182	6	250	14744

183	6	300	14694
184	6	350	14644
185	6	400	14594
186	12	25	14963
187	12	50	14938
188	12	100	14888
189	12	150	14838
190	12	200	14788
191	12	250	14738
192	12	300	14688
193	12	350	14638
194	12	400	14588
195	12	500	14488
196	24	25	14951
197	24	50	14926
198	24	100	14876
199	24	150	14826
200	24	200	13876
201	24	250	13826
202	24	300	13776
203	6	25	9969
204	6	50	9944
205	6	100	9894
206	6	150	9844
207	6	200	9794
208	6	250	9744
209	6	300	9694
210	12	25	9963
211	12	50	9938
212	12	100	9888
213	12	150	9838
214	12	200	9788
215	12	250	9738
216	12	300	9688